REMARKS

Reconsideration and allowance are respectfully requested.

Claims 1, 3-14 and 18-28 are pending. The amendments are fully supported by the original disclosure and, thus, no new matter is added by their entry.

Applicants will be submitting a verified English translation of priority document IT Application No. RM2003A000196, filed on 24 April 2003, in the near future. Such a submission should not be considered untimely because it is not relied upon to antedate a reference cited in the present Section 102/103 rejections.

35 U.S.C. 112 – Definiteness

Claims 1-14 and 17 were rejected under Section 112, second paragraph, as being allegedly "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Applicants traverse.

The meaning of the limitation "an agent endowed with tumor tropism" is understood by those skilled in the art. This meaning is consistent with the specification at page 3, third paragraph, where it is defined as an agent

> "capable of concentrating locally on the tumour cell or in the vicinity of it, immediately prepares, in the residual tissue around the tumour, a sort of receptor of our choosing ready to receive, locally and in an extremely high concentration, the subsequent dose of actual anticancer agent administered intravenously. The anticancer agent must be suitably directed to the site of the tumour, exploiting the affinity of the carrier agent for the receptor artificially created."

In other words, the first agent which is administered locally on the tumor or in the surrounding tissues has the capability (i.e., is "endowed") of attracting by receptor affinity the anticancer agent, which is administered intravenously soon after the operation, toward the tumor site (i.e., tropism).

Applicants request withdrawal of the Section 112, second paragraph, rejection because the pending claims are clear and definite.

35 U.S.C. 102 – Novelty

A claim is anticipated only if each and every limitation as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of Calif.*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). The identical invention must be shown in as complete detail as is claimed. See *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989).

Claims 1, 3-8, 10-13, 17-18 and 20-22 were rejected under Section 102(b) as allegedly anticipated by Goldenberg et al. (U.S. Patent Publ. 2001/0006618). Applicants traverse.

In [0026], Goldenberg discloses a method for the detection or treatment of tumor comprising:

- injecting parenterally a labeled protein (an antibody) which binds to a substance produced or associated with the tumor and
- scanning the interior of the patient with detection means for detecting labeled antibodies.

By contrast, Applicants' claimed invention (see claim 1) is directed to a method for treating tumors comprising:

- locally administering, during the operation, a first agent endowed with tumor tropism and then
- systematically administering, after the operation, the anticancer agent which binds to the first agent.

This method claimed in the present application is neither disclosed nor suggested by Goldenberg because he does not locally administer an agent to bind the labeled protein during the operation as required by Applicants' claim 1.

Withdrawal of the Section 102 rejection is requested because the cited document fails to disclose all limitations of the claimed invention.

35 U.S.C. 103 – Nonobviousness

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing the legal standard provided in *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclosures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case of obviousness requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn*, 78 USPQ2d at 1335; see *KSR*, 82 USPQ2d at 1396. A claim which is directed to a combination of prior art elements "is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." Id. at 1396. Finally, a determination of prima facie obviousness requires a reasonable expectation of success. See *In re Rinehart*, 189 USPQ 143, 148 (C.C.P.A. 1976).

Claims 1-13 and 17-22 were rejected under Section 103(a) as allegedly unpatentable over Goldenberg et al. (U.S. Patent Publ. 2001/0006618) in view of Cokgor et al. (J. Clin. Oncol. 18:3862-3872, 2000). Applicants traverse.

Goldenberg was discussed previously in Applicants' traversal of the Section 102 rejection. In particular, Goldenberg administers the labeled antibody parenterally to the patient. Cogkor discloses that an anticancer agent, which is linked to a labeled antibody, is injected locally into of a surgically created resection cavities (SCRC). In Cogkor, the labeled antibody and the anticancer agent are administered together and at the same moment, i.e. during the intraoperative step (i.e., resection) and locoregionally (i.e., into the SCRC).

By contrast, in the claims of the present application, the method comprises the following:

(a) an agent endowed with tumor tropism, which binds to a molecule specifically produced by the tumour, is administered locoregionally during the surgery then,

(b) an anticancer agent is administered parenterally after the surgery.

Here, the effectiveness of this method of treatment is achieved by the first agent being endowed with the ability to concentrate the anticancer agent at the tumor site. The characterizing feature of the claimed invention is that the first agent endowed with tumor tropism and the anticancer agent are administered separately and at two different stages. Thus, this method allows the administration of the anticancer agent after surgery and ensures that it moves specifically toward the area where the agent endowed with tumor tropism was located during the surgery. In other words, the solution provided by Applicants' invention is using an agent endowed with tumor tropism that specifically localizes the anticancer agent at the tumor site.

The cited documents do not teach or suggest that the agents can be administered separately at different locations (i.e., the first locoregionally and the other parenterally) and at two different moments (i.e., the first during surgery and the other after surgery). In particular, the solution of the claimed invention is not provided by combining Goldenberg with Cogkor because neither of them suggests that the agents can be administered at two different moments. Nor is any reason provided in the Office Action for making such a modification to the combination proposed by the Examiner. One of ordinary skill in the art would also not have a reasonable expectation of success to make such a combination or modification from the cited references and to result in the method claimed in the present application.

Therefore, the claims are not rendered obvious by Goldenberg in view of Cogkor.

Claims 1, 3-8, 10-14, 17-18 and 20-22 were rejected under Section 103(a) as allegedly unpatentable over Goldenberg et al. (U.S. Patent Publ. 2001/0006618) in view of Stendel et al. (Anticancer Res. 24:631-638). Applicants traverse.

Goldenberg was discussed previously in Applicants' traversal of the Section 102 rejection. In Stendel a matrix is sprayed in the tumor area (i.e., SCRC) where taurolidine (i.e., an anticancer agent) is homogenously suspended. The matrix ensures an appropriate delivery locoregionally of the anticancer agent. Stendel discloses that the anti-

cancer agent is administered in the tumor area by dissolving it in a matrix which is locally sprayed. Stendel only adds the concept of spraying locoregionally the agent.

The combination of Goldenberg and Stendel does not suggest the solution provided by Applicants in the present application. Thus, one of ordinary skill in the art would not obtain the solution taught in the present application by combining Goldenberg and Stendel. Therefore, the claims are not rendered obvious by Goldenberg in view of Stendel.

Withdrawal of the Section 103 rejections is requested because the claims would not have been obvious to one of ordinarily skill in the art when this invention was made.

Conclusion

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

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